This part outlines the scientific assessment and knowledge about this product at the time of prequalification. Updates to this information are included in parts 1 to 5 and 8 of this WHOPAR.

SCIENTIFIC DISCUSSION

Name of the Finished Pharmaceutical Product	[HA598 trade name]*
Manufacturer of Prequalified Product	Micro Labs Limited Manufacturing unit: ML-08 15/A, II Phase, Kumbalgodu Industrial Area Bangalore - 560074 Karnataka India
Active Pharmaceutical Ingredient(s) (API)	Sulfamethoxazole/trimethoprim
Pharmaco-therapeutic group (ATC Code)	Antibacterials for systemic use, combinations of sulfonamides and trimethoprim (J01EE01)
Therapeutic indication	[HA598 trade name] is indicated for the treatment and prevention of infections susceptible to sulfamethoxazole/trimethoprim in patients with HIV infection. Such infections include *pneumocystis jiroveci* pneumonitis, toxoplasmosis encephalitis, *plasmodium falciparum* malaria, norcardiosis, brucellosis and certain bacterial infections.

1. Introduction

[HA598 trade name] is indicated for the treatment and prevention of infections susceptible to sulfamethoxazole/trimethoprim in patients with HIV infection. Such infections include *pneumocystis jiroveci* pneumonitis, toxoplasmosis encephalitis, *plasmodium falciparum* malaria, norcardiosis, brucellosis and certain bacterial infections.

[HA598 trade name] should be initiated by a health care provider experienced in the management of HIV infection.

2. Assessment of quality

The assessment was done in accordance with the requirements of WHO's *Guidelines on submission of documentation for a multisource (generic) finished pharmaceutical product for the WHO Prequalification of Medicines Programme: quality part*.

Active pharmaceutical Ingredients (APIs)

CEPs (Certificates of Suitability) issued by the EDQM were submitted for both APIs, ensuring good manufacturing control and applicability of the respective Ph.Eur monographs to control the quality of the APIs. Additional user requirements for both APIs include identification of polymorphic form and particle size distribution.

* Trade names are not prequalified by WHO. This is the national medicines regulatory authority's responsibility.

Other ingredients
Other ingredients used in the tablet formulation include sodium starch glycolate, docusate sodium with sodium benzoate, pregelatinized starch and magnesium stearate. None of the excipients are of animal or human origin and TSE / BSE free attestations have been provided.

Finished pharmaceutical product (FPP)

Pharmaceutical development and manufacture
The multisource product is a white to off-white, flat, circular, bevel-edged, uncoated tablet, with “MICRO” embossed on one side and the other side debossed with "COTRIM” and “480”, with a break line separating the “COTRIM” and "480". The break line is intended for subdivision of tablets when half a tablet dose is to be administered. The tablets are presented in PVC/PVDC-Al blister packs or in a polythene bag within an HDPE bottle. The bottle packs also include sachets filled with silica gel desiccant to protect the tablets from moisture.

Two tablet strengths, proportionally similar in composition, were developed: sulfamethoxazole/trimethoprim 160mg/800mg and 80mg/400mg. The development focussed on the higher strength.

The development of the final composition of the multisource product has been described. The objective was to develop a stable tablet, bioequivalent to the comparator product, Bactrim® DS, which is an immediate release solid dosage form for oral administration. Solid state properties were identified as CQAs for both APIs due to low BCS solubility. The selection of excipients was based on their suitability to achieve the desired tablet characteristics, information on the qualitative composition of the comparator product and compatibility with the APIs. Wet granulation was selected as a method of manufacture of the tablets. Purified water is used as vehicle during wet granulation. During optimization studies the dissolution profiles of the comparator product in BCS related media were targeted. Satisfactory in-process controls have been established.

Specifications
The finished product specifications are pharmacopoeial based and include tests for appearance, identification (IR, HPLC and TLC), average mass, uniformity of mass, tablet dimensions, disintegration time, resistance to crushing, water content (KF), uniformity of dosage units (by content uniformity), dissolution (HPLC detection), assay (HPLC), related substances (HPLC), subdivision of tablets and microbial limits.

Stability testing
Stability studies have been conducted at 30°C/75%RH (zone IVb) as long-term storage conditions and for six months at accelerated conditions in the packaging proposed for marketing of the product. The product proved to be quite stable at these storage conditions, with no negative trends observed. Based on the available stability data, the proposed shelf life and storage conditions as stated in the SmPC are acceptable.

Conclusion
The quality part of the dossier is accepted.

3. Assessment of bioequivalence
The following bioequivalence study has been performed in 2012 according to internationally accepted guidelines.

Study title: An open label, balanced, randomized, two-treatment, two-period, two-sequence, single oral dose, crossover, bioequivalence study of trimethoprim and sulfamethoxazole tablets BP 160 mg / 800

mg with that of Bactrim® DS sulfamethoxazole and trimethoprim (double strength) tablets USP 800 mg/160 mg in healthy, adult, human subjects under fasting condition (study no. 638-12).

The objective of the study was to compare the bioavailability of the stated trimethoprim/sulfamethoxazole FDC tablets manufactured for/by Micro Labs Ltd., India (test drug) with the reference formulation Bactrim® (Mutual Pharmaceutical Co. Inc.) and to assess bioequivalence. The comparison was performed as a single centre, open label, randomized, crossover study in healthy subjects under fasting conditions. Each subject was assigned to receive each of the following treatments in a randomized fashion:

Treatment T: Test – 1 tablet trimethoprim/sulfamethoxazole 160/800 mg (trimethoprim 160 mg + sulfamethoxazole 800 mg) Batch no. TSBBK0001

Treatment R: Reference – 1 tablet Bactrim® (trimethoprim 160 mg + sulfamethoxazole 800 mg) Batch no. 64083

An 8-day wash-out period was observed between administration of test and reference. Serial blood samples (1 pre-dose sample and 25 samples within 72 hours post dose) were taken during each study period to obtain bioavailability characteristics AUC, C_{max} and t_{max} for bioequivalence evaluation. Drug concentrations for trimethoprim and sulfamethoxazole were analyzed using a validated LC-MS/MS method. The limit of quantification was stated to be about 10 ng/mL for trimethoprim and 102 ng/mL for sulfamethoxazole.

The study was performed with 36 participants. Data generated from a total of 34 subjects were utilized for analysis to establish pharmacokinetic parameters and assess bioequivalence.

Arithmetic mean and geometric mean values of the pharmacokinetic variables for trimethoprim and sulfamethoxazole as well as statistical results are summarised in the following tables:

Trimethoprim

Pharmacokinetic Parameter	**Test formulation (T) arithmetic mean ± SD (*)**	**Reference (R) arithmetic mean ± SD (*)**	**log-transformed parameters**	
			Ratio T/R (%)	**Conventional 90% CI (ANOVAlog)**
t_{max} (h)#	2.0 (0.67 – 4.5)	1.67 (0.67 – 12.0)	-	-
C_{max} (ng/mL)	1689 ± 388 (1648)	1682 ± 477 (1619)	102	96 – 108
AUC_{0-t} (ng.h/mL)	26812 ± 6372 (25924)	26674 ± 6755 (25924)	100	97 – 103
AUC_{0-inf} (ng.h/mL)	27367 ± 6636 (26439)	27198 ± 6853 (26432)	100	97 – 103

* geometric mean; # median (range)

Sulfamethoxazole

Pharmacokinetic Parameter	**Test formulation (T) arithmetic mean ± SD (*)**	**Reference (R) arithmetic mean ± SD (*)**	**log-transformed parameters**	
			Ratio T/R (%)	**Conventional 90% CI (ANOVAlog)**
t_{max} (h)#	2.33 (1.0 – 4.5)	2.33 (0.67 – 6.0)	-	-
C_{max} (ng/mL)	65887 ± 12812 (64792)	62355 ± 18870 (59587)	109	101 – 117
AUC_{0-t} (ng.h/mL)	812625 ± 138608	787720 ± 184227	104	99 – 109

	(799692)	(768476)		
$AUC_{0\text{-}inf}$ (ng.h/mL)	818088 ± 139061 (805193)	792584 ± 184916 (773309)	104	99 – 110

* geometric mean; # median (range)

The results of the study show that preset acceptance limits of 80-125 % are met by both AUC and C_{max} values regarding trimethoprim and sulfamethoxazole. Accordingly, the test FDC tablet trimethoprim/sulfamethoxazole 160 mg/800 mg meets the criteria for bioequivalence with regard to the rate and extent of absorption and is therefore, bioequivalent to the reference Bactrim® (Mutual Pharmaceutical Co. Inc.).

A biowaiver was granted for the additional 80 mg/400 mg FDC tablet strength (Micro Labs Ltd., India) in accordance to WHO guidelines. In comparison with the strength of the test product used in the bioequivalence study, the trimethoprim/sulfamethoxazole 80 mg/400 mg tablet was determined to be essentially the same qualitatively with respect to the ratio of active ingredient and excipients. In addition, the dissolution profiles of these two formulations were determined the same for both APIs.

4. Summary of product safety and efficacy

[HA598 trade name] has been shown to conform to the same relevant standards of quality, efficacy and safety as those required of the comparator product. Trimethoprim and Sulfamethoxazole Tablets BP 80 mg/400 mg fulfilled all criteria for waiving an in-vivo bioequivalence study as per relevant WHO guidance. The clinical safety of [HA598 trade name] is considered acceptable when guidance and restrictions stated in the summary of product characteristics (SmPC) are considered. Refer to the SmPC (WHOPAR part 4) for data on clinical safety.

5. Benefit risk assessment and overall conclusion

Quality
Physicochemical and biological aspects relevant to the uniform pharmaceutical characteristics have been investigated and are controlled in a satisfactory way. The quality of this product is considered to lead to an acceptable clinical performance when [HA598 trade name] is used in accordance with the SmPC.

Bioequivalence
[HA598 trade name] fulfilled all criteria for waiving an in-vivo bioequivalence study as per relevant WHO guidance.

Efficacy and Safety
Regarding clinical efficacy and safety, [HA598trade name] is considered effective and safe to use when the guidance and restrictions in the SmPC are taken into consideration.

Benefit Risk Assessment
Based on WHO's assessment of data on quality, bioequivalence, safety and efficacy the team of assessors considered that the benefit–risk profile of [HA598 trade name] was acceptable for the following indication: ‘for the treatment and prevention of infections susceptible to sulfamethoxazole/trimethoprim in patients with HIV infection', and would allow inclusion of [HA598 trade name], manufactured at Micro Labs Limited, Manufacturing Unit: ML-08, 15/A, II Phase, Kumbalgodu Industrial Area, Bangalore – 560074, Karnataka, India in the list of prequalified medicinal products.